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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/884,586	06/19/2001	Yann Echelard	10275-120001 / GTC-31 US	2580
31904	7590	04/19/2006	EXAMINER NGUYEN, QUANG	
GTC BIOTHERAPEUTICS, INC. 175 CROSSING BOULEVARD, SUITE 410 FRAMINGHAM, MA 01702			ART UNIT 1633	PAPER NUMBER

DATE MAILED: 04/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No. 09/884,586	Applicant(s) ECHELARD ET AL.	
	Examiner Quang Nguyen, Ph.D.	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 27 January 2006.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 10,13 and 32-40 is/are pending in the application.
- 4a) Of the above claim(s) 10 and 13 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 32-40 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

Applicant's amendment filed on 1/27/06 was entered for the purpose of a compact prosecution even though it is technically not compliant with the requirements of 37 CFR 1.121 (c) because double brackets are only used to delete five or fewer consecutive characters. The deleted phrase "The method of claim 8," appears to contain 6 consecutive characters.

Claims 10, 13 and 32-40 are pending in the present application.

This application contains claims 10 and 13, drawn to an invention nonelected with traverse in the reply dated 11/05/02. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Accordingly, amended claims 32-40 are examined on the merits herein.

### ***Response to Applicant's amendment***

The rejection under 35 U.S.C. 112, second paragraph, was withdrawn in light of Applicant's amendment.

### ***Claim Objections***

Claims 32-33 are objected to because of the phrase "at least 30% of the PDGF is present in the milk is in a physiologically active dimmer form" is grammatically incorrect. Appropriate correction is required.

Claims 37 and 38 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 39 and 40, respectively. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 35-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. ***This is a new ground of rejection necessitated by Applicant's amendment.***

Claim 35 recites the limitation "said fertilized egg cell" in line 2 of the claim. There is insufficient antecedent basis for this limitation in the claim. This is because prior to this limitation, only fertilized egg and not fertilized egg cell is recited. For the purpose of a compact prosecution, Examiner interprets the claim referring to the same fertilized egg.

Claim 36 recites the limitation "said promoter sequence" in line 2 of the claim. There is insufficient antecedent basis for this limitation in the claim. This is because prior to this limitation, only promoter and not promoter sequence is recited. For the purpose of a compact prosecution, Examiner interprets the claim referring to the same

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promoter. Additionally, it is noted that the terms "caseins", "beta-lactoglobulin" and "lactalbumin" are not promoters. Applicants probably intend to claim casein promoter, beta-lactoglobulin promoter and lactalbumin promoter. The metes and bounds of the claim as written are not clearly determined.

Claims 37-40 recite the limitation "said first and said second sequences" in lines 1 and 2 of the claims. There is insufficient antecedent basis for this limitation in the claim. This is because in neither claim 32 or 33 from which these claims are dependent on, there is no recitation of any first or second sequence. What are the relevant of these first and second sequences in the methods of claims 32 and 33? Additionally, it is unclear what is encompassed by the phrase "are inserted together". Inserted into what? Inserted into a fertilized egg or inserted into a nucleic acid construct? Therefore, the metes and bounds of the claims are not clearly determined.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

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under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended claims 32-34 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Houdebine et al. (U.S. Patent No. 5,965,788) in view of Eichner et al. (U.S. Patent No. 5,665,567; IDS) and Yansue et al. (U.S. Patent No. 5,834,269). ***This is a new ground of rejection necessitated by Applicant's amendment.***

Houbedine et al. teaches a method of producing a transgenic non-human mammal whose genome comprises a DNA construct comprising a rabbit WAP promoter directing the expression of a DNA sequence encoding a heterologous protein. Houbedine et al. also teaches methods of using the transgenic non-human mammal in the production of recoverable amounts of a heterologous protein in the mammal's milk, and that the mammal is a bioreactor for a protein of interest (see abstract and the claims). Houdebine et al. listed different heterologous proteins to be expressed such as growth factors, interleukins, stimulating factors, kinases, coagulation factors among others (see col. 4), and various promoters (e.g., alpha-casein, beta-casein, beta-lactoglobulin, WAP) that have been used to make transgenic non-human mammals expressing heterologous protein in their milk (see Table 1). Houdebine et al. also teaches that the DNA constructs are introduced by microinjection into fertilized eggs at the one cell up to the 8-cell stage in the making of the transgenic non-human mammals (see col. 2, lines 57-61).

Houdebine et al. does not specifically teach a method of producing a transgenic non-human mammal capable of expressing an active PDGF molecule in its milk utilizing a nucleic acid construct containing an insulator sequence inserted on either side of a nucleic acid sequence encoding a PDGFchain, even though Houdebine et al teaches a method of producing any heterologous protein, including any growth factor, in the milk of any female, non-human transgenic mammal.

However, at the effective filing date of the present application, Eichner et al. teaches that cDNA clones encoding for the PDGF-A chain and PDGF-B chains are available and that different routes for preparing recombinant PDGF homodimers are known (see col. 3, lines 32-53; col. 4, lines 34-38). Additionally, recombinant PDGF-AB heterodimers have been prepared in eukaryotic expression systems wherein both PDGF-A and PDGF-B genes are located on one vector in independent transcription units (col. 4, lines 48-59). Eichner et al. further teaches that it is known in the literature that when both PDGF genes are expressed in a eukaryotic cell, 30% or more of the produced PDGF is in the form of a homodimer (col. 5, lines 5-9). Eichner et al. further discloses the use of a bicistronic expression vector system in which an IRES sequence is located between the first and second cistrons and in which the PDGF-B chain coding gene is located in the first cistron to produce predominantly recombinant PDGF-AB heterodimers (see abstract and the claims). The PDGF-species are involved in the wound healing process, and the most frequent isoform PDGF-AB has been taught by Eichner et al. to be formulated in a pharmaceutical preparation for wound healing, for

skin regeneration, skin smoothening, for preventing of scaring or of skin ageing or for sunburn (see col. 3, line 64 continues to line 2 of col. 4; col. 7, lines 46-62).

Yasue et al. also teaches that an exogenous gene that is introduced into a fertilized egg should be placed between insulators so as to ensure an insulated environment, such that the introduced exogenous gene will not be affected by any influence from adjacent genes in the fertilized egg and thus allowing correct expression of introduced exogenous gene to produce desired transgenic organism (see Summary of the Invention).

Accordingly, it would have been obvious and within the scope of a skilled artisan to modify the method taught by Houdebine et al. by introducing a nucleic acid sequence encoding a PDGF-A chain and/or a PDGF-B chain either in separate nucleic acid molecules or in a bicistronic expression vector (depending on the PDGF species desired) into a fertilized egg, wherein the nucleic acid sequence is operatively linked to a promoter which directs the expression of a PDGF mammary gland epithelial cells, and wherein the nucleic acid sequence is flanked by insulator sequences in light of the teachings of Eichner et al. and Yasue et al. to produce a non-human transgenic mammal capable of expressing an active PDGF molecule in its milk.

An ordinary skilled artisan would have been motivated to carry out the above modification because the mitogenic PDGF-species are involved in the wound healing process. Therefore, there was a need in the prior art at the effective filing date of the present application for obtaining a significant quantity of purified and biologically active PDGF-species for the preparation of pharmaceutical compositions. Furthermore,



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Houdebine et al. already teaches that the production of a recombinant protein secreted in the milk of a non-human transgenic mammal provides a highly desirable system for obtaining the recombinant protein in large quantities, in mature state due to proper glycosylation, phosphorylation and enzymatic processing, as well as the relative ease of collecting and recovering the recombinant protein in milk (see col. 1, lines 30-41). Additionally, as taught by Yasue et al., the utilization of insulator sequences flanking the nucleic acid sequence encoding PDGF would eliminate any influence from adjacent genes in a genome of the transgenic non-human mammal and thus allowing correct expression of active PDGF in mammary glands to produce an active recombinant PDGF in milk.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Houdebine et al., Eichner et al. and Yasue et al., coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

### ***Response to Amendment***

Applicants' arguments related to the above rejection in the Amendment filed on 1/27/06 (pages 7-12) have been fully considered, but they are not found to be persuasive.

1. Applicants argue mainly that the Houdebine et al. discloses a conventional method of producing a transgenic animal but neither claims the production of a growth

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factor such as PDGF, nor offers any specific teaching with regard to this type of molecule in a whole animal setting; and Eichner et al. does not provide what Houdebine et al. lacks. Applicants further argue that the Eichner et al. reference is a non-analogous art because Eichner et al. fails to provide any discussion of any expression system other than *in vitro* cell culture conditions and therefore it fails to understand or make obvious the true nature of the present invention. Applicants further argue that the combination of the cited references is a result of an improper hindsight, and that the cited disclosures do not explicitly contain all the necessary techniques and suggest the combination that would lead to the invention as claimed.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is noted that Applicants did not take into considerations both teachings of Houdebine et al and Eichner et al together.

In response to applicant's argument that the Eichner et al. is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, Eichner et al. teaches clearly that cDNA clones encoding for the PDGF-A chain and PDGF-B chains are available and that different routes for preparing

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active recombinant active PDGF homodimers as well as PDGF heterodimers for preparation of pharmaceutical compositions containing PDGF species. Although Eichner et al does not explicitly discuss any expression system other than the *in vitro* cell culture expression systems, there was a clear need in the prior art at the effective filing date of the present application for obtaining a significant quantity of purified and biologically active PDGF-species for the preparation of pharmaceutical compositions. Also at the effective filing date of the present application, Houdebine et al. teaches clearly that the production of a recombinant protein, including any growth factors, secreted in the milk of a non-human transgenic mammal provides a highly desirable system for obtaining the recombinant protein in large quantities, in mature state due to proper glycosylation, phosphorylation and enzymatic processing, as well as the relative ease of collecting and recovering the recombinant protein in milk (see col. 1, lines 30-41). Therefore, the Eichner et al. reference is reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA

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1971). Eichner et al. teaches advantages and needs for the production of PDGF-AA, PDGF-BB, PDGF-AB. Houdebine et al. teaches clearly that a non-human transgenic mammal provides a highly desirable system for obtaining a recombinant protein in large quantities (e.g., growth factors), in mature state due to proper glycosylation, phosphorylation and enzymatic processing, as well as the relative ease of collecting and recovering the recombinant protein in its milk (see col. 1, lines 30-41).

In response to Applicant's argument implying that the combination of the cited teachings has no reasonable expectation of success, Examiner notes that Houdebine et al. has successfully produce numerous heterologous proteins (e.g., erythropoietin, G-CSF, I1-antitrypsin, urokinase, hirudin, factor VIII, any growth factor, any interleukin, any kinases, as well as any coagulation factors) in any non-human mammal's milk. Applicants have not provided any scientific reasons why an ordinary skilled artisan would not have a reasonable expectation of success for expressing biological active PDGF in milk of a transgenic non-human mammal, given a high level of skills of an ordinary skilled artisan at the effective filing date of the present application for producing a heterologous protein in milk of a transgenic non-human mammal.

2. With respect to the issue that the Eichner et al. reference is a non-analogous art, Applicants cited Wang Laboratories, Inc. v. Toshiba Corp. 26 U.S.P.Q. 2d 1767 (Fed. Cir. 1993) and King Instrument Corp. v. Otari Corp., 226 U.S.P.Q. 402, 405 (Fed. Cir. 1985). Applicants argued that as in the Wang and King situations, the instant claimed invention is directed to features, methods and solutions of problems

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which are alien and non-analogous to the teachings of Eichner et al reference which focuses and provides teaching with regard only to simple expression in eukaryotes rather in transgenic animals with an entirely different set of concerns and hurdles preventing success than those inherent in the instant invention. Therefore, the Eichner et al. reference falls outside the scope of appropriate art and making itself unavailable for combination with Houdebine to render the amended claims obvious.

Once again, Applicant's arguments are directed solely on the Eichner et al reference, without given any consideration for the primary reference of Houdebine et al. Please note that the rejection is a 103 rejection, and therefore Eichner et al does not have to teach PDGF expression in a transgenic non-human mammal. All the concerns or hurdles for expressing a protein in a transgenic animal have been successfully addressed by the teachings of Houdebine et al. It is further noted that PDGF is a growth factor and Houdebine et al teaches a method of producing any heterologous protein, including any growth factor, in the milk of any female, non-human transgenic mammal.

Accordingly, amended claims 32-34 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Houdebine et al. (U.S. Patent No. 5,965,788) in view of Eichner et al. (U.S. Patent No. 5,665,567; IDS) and Yansue et al. (U.S. Patent No. 5,834,269) for the reasons set forth above.

Claim 35 is rejected under 35 U.S.C. 103(a) as being unpatentable over Houdebine et al. (U.S. Patent No. 5,965,788) in view of Eichner et al. (U.S. Patent No.

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5,665,567; IDS) and Yansue et al. (U.S. Patent No. 5,834,269) as applied to claims 32-34 and 36 above, and further in view of either Lubon et al. (US 5,880,327) or Meade et al. (US 5,849,92). ***This is a new ground of rejection necessitated by Applicant's amendment.***

The combined teachings of Houdebine et al., Eichner et al. and Yansue et al. are presented above. However, none of the reference teaches specifically that the used fertilized egg is obtained from an ungulate from the recited Markush group of claim 35, even though Houdebine et al teaches clearly a method of producing any heterologous protein, including any growth factor, in the milk of any female, non-human transgenic mammal.

However, at the effective filing date of the present application Lubon et al also taught the preparation of a transgenic ungulate such as pig, cattle, goat, horse, sheep that produces in its mammary gland cells and secretes into its milk a recombinant human Factor VIII protein or fragment or modification thereof having physiological activity of human Factor VIII by introducing DNA encoding said Factor VIII protein or fragment or modification thereof into the aforementioned fertilized mammalian ova (see at least col. 4, lines 29-44; and the claims). Similarly, Meade et al also disclosed the preparation of a transgenic ungulate such as cow, camel, sheep, goat and pig that produces monoclonal antibodies in its milk by introducing DNAs encoding said monoclonal antibodies into the aforementioned fertilized ungulate ova (see at least col. 4, lines 19-36; and the claims).

Accordingly, it would have been obvious for an ordinary skilled artisan to further modified the combined teachings of Houdebine et al., Eichner et al. and Yansue et al. by using a fertilized egg obtained from an ungulate such as a pig, cattle, a goat, a horse or a sheep to produce a non-human transgenic mammal expressing an active PDGF molecule in its milk in light of either the teachings of Lubon et al. or Meade et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because the production of such recombinant ungulates would result in the attainment of large amount of recombinant milk containing active recombinant PDGF over long periods of time (see at least Meade et al.; col. 4, lines 24-25).

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Houdebine et al., Eichner et al., Yasue et al., and either Lubon et al. or Meade et al., coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

### **Conclusions**

#### ***No claims are allowed.***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's primary, Celine Qian, Ph.D., may be reached at (571) 272-0777, or SPE, Dave Nguyen, at (571) 272-0731.

**To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.**

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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CELINE QIAN, PH.D.  
PRIMARY EXAMINER

